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(21) International Application Number: PCT/US97/21636 (22) International Filing Date: 5 December 1997 (05.12.97) (30) Priority Data: <table border="0"><tr><td>08/761,190</td><td>6 December 1996 (06.12.96)</td><td>US</td></tr><tr><td>08/762,381</td><td>6 December 1996 (06.12.96)</td><td>US</td></tr><tr><td>08/771,317</td><td>6 December 1996 (06.12.96)</td><td>US</td></tr><tr><td>08/760,916</td><td>6 December 1996 (06.12.96)</td><td>US</td></tr><tr><td>08/761,313</td><td>6 December 1996 (06.12.96)</td><td>US</td></tr><tr><td>08/985,201</td><td>4 December 1997 (04.12.97)</td><td>US</td></tr><tr><td>08/984,881</td><td>4 December 1997 (04.12.97)</td><td>US</td></tr><tr><td>08/985,056</td><td>4 December 1997 (04.12.97)</td><td>US</td></tr><tr><td>08/984,884</td><td>4 December 1997 (04.12.97)</td><td>US</td></tr><tr><td>08/985,298</td><td>4 December 1997 (04.12.97)</td><td>US</td></tr></table> (71) Applicant: CORTECH, INC. [US/US]; 6850 North Broadway, Denver, CO 80221 (US). (71)(72) Applicants and Inventors: GYORKOS, Albert [US/US]; 11795 Decatur Drive, Westminster, CO 80234 (US). SPRUCE, Lyle, W. [US/US]; 948 Camino del Sol, Chula Vista, CA 91910 (US).		08/761,190	6 December 1996 (06.12.96)	US	08/762,381	6 December 1996 (06.12.96)	US	08/771,317	6 December 1996 (06.12.96)	US	08/760,916	6 December 1996 (06.12.96)	US	08/761,313	6 December 1996 (06.12.96)	US	08/985,201	4 December 1997 (04.12.97)	US	08/984,881	4 December 1997 (04.12.97)	US	08/985,056	4 December 1997 (04.12.97)	US	08/984,884	4 December 1997 (04.12.97)	US	08/985,298	4 December 1997 (04.12.97)	US	(74) Agents: BURKE, John, E. et al.; Cushman Darby & Cushman, Intellectual Property Group of Pillsbury Madison & Sutro, 1100 New York Avenue, N.W., Washington, DC 20005 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>	
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(54) Title: SERINE PROTEASE INHIBITORS																																	
(57) Abstract The present invention relates to certain substituted oxadiazole, thiadiazole and triazole peptoids which are useful as inhibitors of serine proteases.																																	

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SERINE PROTEASE INHIBITORS

The present invention relates to certain substituted oxadiazole, thiadiazole and
5 triazole peptoids which are useful as inhibitors of serine proteases.

Background of the Invention

The serine proteases are a class of enzymes which includes elastase, chymotrypsin, cathepsin G, trypsin and thrombin. These proteases have in common a
10 catalytic triad consisting of Serine-195, Histidine-57 and Aspartic acid-102 (chymotrypsin numbering system). Human neutrophil elastase (HNE) is a proteolytic enzyme secreted by polymorphonuclear leukocytes (PMNs) in response to a variety of inflammatory stimuli. This release of HNE and its extracellular proteolytic activity are highly regulated and are normal, beneficial functions of PMNs. The degradative
15 capacity of HNE, under normal circumstances, is modulated by relatively high plasma concentrations of α_1 -proteinase inhibitor (α_1 -PI). However, stimulated PMNs produce a burst of active oxygen metabolites, some of which (hypochlorous acid for example) are capable of oxidizing a critical methionine residue in α_1 -PI. Oxidized α_1 -PI has been shown to have limited potency as an HNE inhibitor and it has been proposed that
20 alteration of this protease/antiprotease balance permits HNE to perform its degradative functions in localized and controlled environments.

Despite this balance of protease/antiprotease activity, there are several human disease states in which a breakdown of this control mechanism is implicated in the pathogenesis of the condition. Improper modulation of HNE activity has been
25 suggested as a contributing factor in adult respiratory distress syndrome, septic shock and multiple organ failure. A series of studies also have indicated the involvement of PMNs and neutrophil elastase in myocardial ischemia-reperfusion injury. Humans with below-normal levels of α_1 -PI have an increased probability of developing emphysema. HNE-mediated processes are implicated in other conditions such as
30 arthritis, periodontal disease, glomerulonephritis, dermatitis, psoriasis, cystic fibrosis, chronic bronchitis, atherosclerosis, Alzheimer's disease, organ transplantation, corneal ulcers, and invasion behavior of malignant tumors.

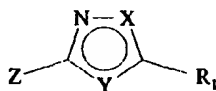
There is a need for effective inhibitors of HNE as therapeutic and as

prophylactic agents for the treatment and/or prevention of elastase-mediated problems.

Summary of the Invention

5 The present invention provides compounds which are useful as serine protease inhibitors, including human neutrophil elastase. These compounds are characterized by their relatively low molecular weight, high potency and selectivity with respect to HNE. Additionally, certain compounds of the invention have demonstrated oral
10 bioavailability as exhibited by their higher blood levels after oral dosing. Oral bioavailability allows oral dosing for use in chronic disease, with the advantages of self-administration and decreased cost over other means of administration. The compounds described herein can be used effectively to prevent, alleviate or otherwise treat disease states characterized by the degradation of connective tissue by proteases in humans.

15 The present invention provides compounds comprising oxadiazole, thiadiazole or triazole ring structures, and can be generically described by the formula:



wherein Z is a serine protease binding moiety, preferably an elastase binding moiety, and most preferably a human neutrophil elastase binding moiety. Specifically, Z is a carbonyl containing group, preferably an α -amino carbonyl containing group where
20 the carbonyl carbon is covalently attached to the carbon of the heterocycle.

R_1 is alkyl, alkenyl or alkynyl optionally substituted with 1 or more, preferably 1-3, halo, hydroxyl, cyano, nitro, haloalkyl, alkylamino, dialkylamino, alkoxy, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamide, arylcarboxamide or -O-(C₅-C₆)aryl; hydroxyl, amino, alkylamino or dialkylamino; or cycloalkyl, alkylcycloalkyl,
25 alkenylcycloalkyl, cycloalkenyl, alkylcycloalkenyl, alkenylcycloalkenyl, (C₅-C₁₂)aryl, (C₅-C₁₂)arylalkyl, (C₅-C₁₂)arylalkenyl, fused (C₅-C₁₂)aryl-cycloalkyl or alkyl fused (C₅-C₁₂)aryl-cycloalkyl optionally comprising 1-4 heteroatoms selected from N, O and S, and optionally substituted with halo, cyano, nitro, hydroxyl, haloalkyl, amino, aminoalkyl, dialkylamino, alkyl, alkenyl, alkylenedioxy, alkynyl, alkoxy, haloalkoxy,
30 carboxyl, carboalkoxy, alkylcarboxamide, (C₅-C₆)aryl, -O-(C₅-C₆)aryl,